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Cost and Effectiveness Evaluation of Prophylactic HPV Vaccine in Developing Countries

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ABSTRACT

Background: Approximately 80% of cervical cancer cases occur in developing countries. In Thailand, cervical cancer has been the leading cancer in females, with an incidence of 24.7 cases per 100,000 individuals per year. **Objectives:** We constructed a decision model to simulate the lifetime economic impact for women in the context of human papillomavirus (HPV) infection prevention. HPV-related diseases were of interest: cervical cancer, cervical intraepithelial neoplasia, and genital warts. The two strategies used were 1) current practice and 2) prophylactic quadrivalent vaccine against HPV types 6, 11, 16, and 18. **Methods:** We developed a Markov simulation model to evaluate the incremental cost-effectiveness ratio of prophylactic HPV vaccine. Women transition through a model either healthy or developing HPV or its related diseases, or die from cervical cancer or from other causes according to transitional probabilities under the Thai health-care context. Costs from a provider perspective were obtained from King Chulalongkorn Memorial Hospital. Costs and benefits were discounted at 3% annually. **Results:** Compared with no prophylactic HPV vaccine, the incremental cost-effectiveness ratio was 160,649.50 baht per quality-adjusted life-year. The mortality rate was reduced by 54.8%. The incidence of cervical cancer, cervical intraepithelial neoplasia grade 1, cervical intraepithelial neoplasia grade 2/3, and genital warts was reduced by up to 55.1%. **Conclusion:** Compared with commonly accepted standard thresholds recommended by the World Health Organization Commission on Macroeconomics and Health, the nationwide coverage of HPV vaccination in girls is likely to be cost-effective in Thailand.

Keywords: cost-effectiveness, developing countries, HPV vaccine.

Introduction

Cervical cancer is the second most common female malignancy worldwide. Approximately 80% of all cases occur in developing countries and predominantly in low socioeconomic populations [1–4]. Results from many studies suggest that infection with human papillomavirus (HPV) is the first step in the development of cervical cancer [5–7]. There are more than 100 types of papilloma viruses (HPVs) that infect humans. Types 16 and 18 were the most common types identified in patients with cervical cancer in Western countries (70%–85% of cases) [8–13].

In Thailand, cervical cancer has been the leading cancer in females, accounting for 24.7 new cases per 100,000 individuals per year [14,15]. Furthermore, cervical cancer has been identified as a national public-health problem [16,17]. Among a population of 32.2 million women in 2008, there were an estimated 8000 new cases and about 2178 deaths [18,19]. HPV types 16 and 18 account for 52% and 19% of cervical cancers, respectively [20]. HPV type 16 was detected in 48% and type 18 in 16% of individuals with cervical intraepithelial neoplasia (CIN) grade 3 [21].

On the basis of this evidence, great effort has been undertaken to develop effective HPV vaccines [22]. Currently, HPV vaccines have been approved worldwide for preventing cervical cancer and other HPV-related diseases [23]. Several mathematical models based on the natural history of HPV diseases have been published to evaluate the cost-effectiveness of the HPV vaccine [12,24–33]. This study used a different approach. We modeled a treatment algorithm reflecting standard practice for individuals with genital warts, CIN1, CIN2/3, as well as cervical cancer and compared the effect that vaccine would have on the population of patients who did and did not receive prophylactic HPV vaccination.

Objectives

We therefore aimed to perform a cost-effectiveness evaluation of a prophylactic HPV (6, 11, 16, 18) vaccination program compared with current management from a care provider perspective under the Thai health-care management setting as the nominated comparator.

Methods

Simulation model

We developed a mutually exclusive state-transition Markov model [34,35] to clearly depict the clinical management algorithm of treatments for genital warts, CIN, and various stages of cervical cancer (Fig. 1) as defined by the Federation of Gynaecology and

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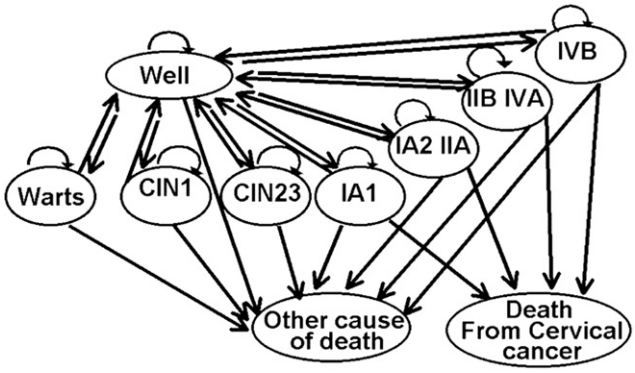

Fig. 1 – Simple schematic model to portray the algorithm of treatments of genital warts, cervical intraepithelial neoplasia (CIN), and stages for cervical cancer. CIN, cervical intraepithelial neoplasia; IA1, cervical cancer stage IA1; IA2–IIA, cervical cancer stage IA2–IIA; IIB–IVA, cervical cancer stage IIB–IVA; IVB, cervical cancer stage IVB.

Obstetrics using the TreeAge software (TreeAge software, Inc., Williamstown, MA). Our hypothetical longitudinal entire lifetime cohort was 12-year-old girls who never had sexual intercourse. The cohort was followed through different health states until age 100 years. In yearly cycles, each girl had her own outcome and moved through health states. Women could transition healthy or develop HPV and its related diseases as a result of diagnosis, or they could die from cervical cancer or other causes according to transitional probabilities. In an attempt to decrease bias and improve the quality of the data used to calculate the transition probabilities required by the model, the authors reviewed the literature thoroughly and systematically for data on Thai health outcomes. When adequate Thai data were not available, we used data from the Asia-Pacific or other regions and experts' opinion.

The age-specific incidence of cervical cancer was obtained from the National Cancer Institute, Ministry of Public Health (MoPH), Thailand. The number of noncervical cancer deaths was estimated by using Thai female lifetable statistics [36]. Data are shown in Table 1.

Assumptions

The main assumptions of the model were as follows:

1. Vaccination was at the age of 12 years.
2. The proportion of women taking immunization was 100% and varied in the sensitivity analysis.
3. The duration of vaccine protection was lifelong, with a vaccination cost of 6189 Thai baht per three-dose course.
4. The efficacy of the quadrivalent vaccine against HPV types 6, 11, 16, and 18, based on literature review, was estimated at 97% [53]. In the sensitivity analyses, alternative assumptions were investigated by varying this efficacy from 90% to 99.9% and cross-protection between types was not taken into account.
5. Because the Markov Model did not have the ability to remember prior events, we assumed that women who were treated and were cured returned to the healthy state and had a probability of redeveloping a disease similar to those of women without prior disease.
6. The Federation of Gynaecology and Obstetrics stages classification and treatment algorithm would not change over time.

Cost of care

To assess the costs of care, we conducted the analysis from the perspective of a health-care provider. Costs, expressed in Thai

Table 1 – Baseline values in the model.

Variable	Base case	Reference
Annual probability of death (from all causes)		[36]
10–14*	0.001	
50–54	0.0134	
95–99	0.8103	
Annual incidence of cervical cancer	24.7 per 100,000	[37]
15–19*	1 per 100,000	
50–54	74 per 100,000	
70–74	61 per 100,000	
Annual incidence of CIN1	120 per 100,000	[38]
15–19*	160 per 100,000	
20–24	510 per 100,000	
>70	20 per 100,000	
Annual incidence of CIN2/3	80 per 100,000	[38]
15–19*	90 per 100,000	
25–29	380 per 100,000	
>70	1 per 100,000	
Annual incidence of genital warts	231 per 100,000	[39]
10–14*	10 per 100,000	
20–24	861 per 100,000	
>45	48 per 100,000	
5-y cancer survival (%)		
Stage IA1	94.3	[40]
Survival of recurrence	93.7	[41]
Stage IA2, IB, IIA	88.8	[42]
Survival of recurrence	83.3	[41]
Stage IIB–IVA	67.6	[43]
Survival of recurrence	53.0	[43]
Stage IVB	22	[44]
5-y progression-free survival (%)		
Stage IA1	92	Assumed
Stage IA2, IB, IIA	80	[45]
Stage IIB–IVA	6	Assumed
Median progression-free survival: Stage IVB (mo)	3.8	[46]
Annual recurrence rate: CIN1 (%)	9	[47]
Annual recurrence rate: CIN2/3 (%)	11.9	[48]
Annual recurrence rate: genital warts (%)	39	[49]
Prevalence of HPV16 or 18 in CIN (%)	75	[21]
Prevalence of HPV16 or 18 in cervical cancer (%)	85.5	[50]
Prevalence of HPV6 or 11 in genital warts (%)	80	[51]
Quality of life of patients with	Mean (SD)	[52]
Genital warts	0.743 (0.12)	
CIN1	0.787 (0.09)	
CIN2/3	0.776 (0.13)	
IA1	0.784 (0.13)	
IA2, IB, IIA	0.788 (0.13)	
IIB–IVA	0.776 (0.13)	
IVB	0.814 (0.12)	

CIN, cervical intraepithelial neoplasia; IA1, cervical cancer stage IA1; IA2, cervical cancer stage IA2; IB, cervical cancer stage IB; IIA, cervical cancer stage IIA; IIB–IVA, cervical cancer stage IIB–IVA; IVB, cervical cancer stage IVB.

* Calculate in 5-y age categories; only lowest, middle, and highest age groups were showed.

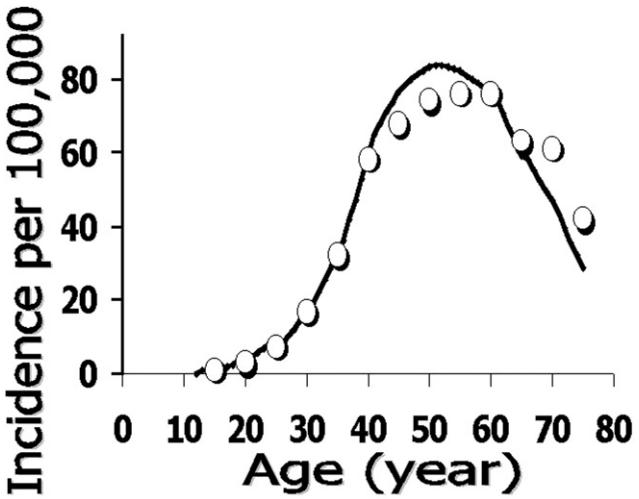

Fig. 2 – Model validity. Comparison of model-predicted and observed data for age-specific incidence of cervical cancer. Solid line represents the model prediction of cervical cancer in Thailand. Circle represents Thailand incidence data obtained from the National Cancer Institute, Ministry of Public Health [56].

baht, in this study were given from the unit costs analysis, which were provided by the Center of Health Assurance at King Chulalongkorn Memorial Hospital (Table 3). The medical costs associated with each procedure were separated into major categories: cost of treatment of genital wart and cost of treatment of cervical cancer (composed of medical treatment and surgical treatment as well as costs for chemotherapy and radiotherapy administration, and cost of palliative treatment for those patients who need supportive care). Capital cost and labor cost were already included in the unit cost for inpatient and outpatient services.

Costs in baht were converted to US dollar by using the exchange rate of 35 bahts per dollar.

Benefit

The qualitative measure of health utilities ranged from a minimum of 0 (death) to a maximum of 1 (perfect health). For long-term cost utility analysis, we used quality of patient's life (Table 1) obtained from our previous study [52] and enumerated in quality-adjusted life-years.

Future costs and benefit were discounted at an annual rate of 3.0% [54]. The results of cost-effectiveness analysis were summarized by the use of incremental cost-effectiveness ratios (ICERs).

Sensitivity analysis

We conducted sensitivity analyses via Monte Carlo simulation to evaluate the robustness of our conclusions over a range of important parameters. Beta distribution was used to calculate any probabilities, and Gamma distribution was applied to unit costs in probabilistic sensitivity analysis.

Because of the skewness in cost distribution, the ranges of costs were varied 10% below and three times above the base-case estimation.

The cost of the vaccine was also varied to include the range of values that have been used in a previous study [55].

For clinical variables, the range of variations likely to be encountered in the clinical setting was based on discussions with experts. In one sensitivity analysis, 10,000 model simulations were completed.

Model validity

To validate the model, we compared the incidence of cervical cancer cases and deaths predicted by our Markov model with those reported by the National Cancer Institute and the MoPH (Fig. 2). Our model had a shape and a peak that were similar to those reported. The incidence rate according to the model was 24.3 per 100,000, which is slightly less than but very close to the incidence rate given by the MoPH (24.7 per 100,000).

The model gave a cervical cancer mortality rate of 7.99 per 100,000. The crude death rate given by the MoPH was 5.2 per 100,000 for the year 2007.

Results

Base-case-analysis and sensitivity analysis

Under the base-case scenario, a prophylactic HPV vaccine for 12-year-old girls was more expensive than current practice but also resulted in greater quality-adjusted life-year (Table 2). The ICER was 160,649.50 bahts per quality-adjusted life-year.

HPV vaccine reduces the lifetime number of cervical cancer cases and deaths by 55%. Furthermore, cases of CIN1, CIN2/3, and genital warts were reduced by 51% to 54% (Table 2). One-way sensitivity analysis was performed around the range of unit costs, vaccine price, discount rate, quality of life, and parameters as outlined in Table 3. Changes in clinical variables altered the amount of ICER but did not alter the conclusions. Not surprisingly, the cost-effectiveness ratio was sensitive to changes in vaccine price and percentage of girls covered by the vaccination program. The model showed that the ICER was beyond the usual accepted

Table 2 – Difference between vaccinated and unvaccinated cohort of 100,000 women at base-case parameters.

	Vaccinated	Unvaccinated
Total costs of cohort (baht)	803,464,334.7	398,873,486.4
	SD* = 78,059,309.5	SD* = 173,033,801.8
Incremental cost (baht)		404,590,848.3
Total QALY of cohort	2,659,620.8	2,657,102.3
	SD* = 6,678.4	SD* = 15,341.6
Incremental QALY		2,518.5
ICER (baht/QALY)		160,649.5
Health outcomes		
Cervical cancer incidence	10.9/100,000	24.3/100,000
Reduction (%)		55.1
Cervical cancer mortality	3.25/100,000	7.19/100,000
Reduction (%)		54.8
Genital wart annual incidence	196.4/100.000	406.18/100.000
Reduction (%)		51.6
CIN1 annual incidence	63.5/100.000	138.85/100.000
Reduction (%)		54.3
CIN 2/3 annual incidence	30.89/100.000	67.08/100.000
Reduction (%)		53.9

CIN, cervical intraepithelial neoplasia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SD, standard deviation.

* SD: standard deviation from Monte Carlo simulation.

Table 3 – Results of sensitivity analysis.

		Price and cost	
		Range for sensitivity analysis	ICER range (baht/QALY)
Vaccine price (baht)		6,189–12,378	160,649–406,394
Unit cost for procedure (baht)			
Medical treatment of warts	3348.24	3,013–10,045	161,990–133,881
Surgical treatment of warts	5,941.56	5,347–17,825	160,887–155,900
Cryotherapy	638.10	574–1,914	160,661–160,413
Conization	33,805.70	30,425–101,417	163,574–102,169
Total abdominal hysterectomy	39,842.29	35,858–119,527	161,522–143,196
Radical hysterectomy	101,830.80	91,648–305,492	161,117–151,293
Vaginectomy	39,156.97	35,241–117,471	160,698–159,670
Chemotherapy	270,857.28	243,772–812,572	161,487–143,900
Radiation	52,575.45	47,318–157,726	161,103–151,570
Palliative care	66,142.96	59,529–189,429	161,966–136,104
Discount rate (%)			
Both costs and outcomes		2.5–6.0	152,092–295,038
Utility rate (QOL value for)			
Genital warts		0.60–0.80	51,688–1,005,734
CIN1		0.60–0.80	66,313–178,281
CIN2/3		0.60–0.80	83,608–183,737
IA1		0.60–0.80	154,044–161,251
IA2, IB, IIA		0.60–0.80	150,602–161,337
IIB–IVA		0.60–0.80	154,815–161,479
IVB		0.60–0.85	160,069–160,748
Efficacy of vaccine (%)		90.0–99.9	292,115–133,352
Vaccine coverage (%)		80.0–100	394,353–160,649
Effect of human papillomavirus (HPV)			
HPV 16/18 cause of cervical cancer (%)		70.0–90.0	259,103–145,416
HPV 6/11 cause of genital warts (%)		70.0–90.0	221,092–127,794

CIN, cervical intraepithelial neoplasia; IA1, cervical cancer stage IA1; IA2, cervical cancer stage IA2; IB, cervical cancer stage IB; IIA, cervical cancer stage IIA; IIB–IVA, cervical cancer stage IIB–IVA; IVB, cervical cancer stage IVB; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QOL, quality of life.

threshold for cost-effectiveness when the vaccine price was doubled or the vaccine coverage rate was less than 80%. Change in the utility value for genital warts had a considerable impact on the ICER (Table 3).

Discussion

From the cohort of 12-year-old girls going through the Markov model, numerical results were compared for model simulation with and without vaccination. In 2009, the gross national income per capita was US$3,869 per year or 135,415 Thai bahts [57]. According to the standard thresholds recommended by the World Health Organization Commission on Macroeconomics and Health [58], the model showed that HPV vaccination, compared with current management, was likely to be cost-effective in Thailand. The finding of this study agreed with those studies conducted by Goldie et al. [12], Sanders and Taira [32], and Taira et al. [33]. The prophylactic quadrivalent vaccine saved 9 quality-adjusted life-days per person (2,518.5 years per 100,000 persons). Although this is modest at the individual level, the population benefit is comparable to vaccinations against hepatitis B virus, pertussis, rubella, measles, or mumps, which save 3.6, 3.3, 3.0, 2.7, and 0.3 life-days, respectively [59].

Factors that most influenced the cost-effectiveness were the cost of vaccine, the efficacy of vaccine, and the vaccine coverage rate. Sensitivity analysis showed that the HPV vaccine would be cost-effective even assuming the efficacy of vaccine was down to 90%.

Concerning the cost of vaccine, the ICER would be above the recommended thresholds if the vaccine price were to double. In this model, we assumed lifelong immunization. To date, there are no data to suggest that booster doses are needed but if they were, this would increase the vaccine price and decrease its cost-effectiveness [60].

High vaccine uptake rate was necessary to maximize the effectiveness of the prophylactic vaccination. Scenario analysis showed that the more one reduces the vaccine coverage, the less cost-effective the vaccination program was.

This study has limitations that need to be discussed further. First, our study was conducted in a single institution. The information on costs was obtained from King Chulalongkorn Memorial Hospital, which is a large, tertiary, government teaching hospital. This approach would underestimate costs when compared with private hospitals and may overestimate the costs of care in secondary or primary hospitals. To cope with this limitation, we employed Monte Carlo simulation to display the spread of expected values when cost distributions were assigned earlier. Furthermore, in sensitivity analysis, the ranges of the costs were varied 10% below and three times above the base-case estimation.

The second limitation was the lack of country information on age-specific incidence of genital warts and CIN. As such, we had to adopt published data from other countries. Such an approach is not without pitfalls as one over- or underestimates the actual disease incidence. To use the best available information, publications were reviewed and chosen according to the experience of specialists on the subject.

Third, as vaccine efficacy trials have mostly used female subjects [53,61], our hypothetical population were girls. Consequently, herd immunity (i.e., the protective effect on the popula-

tion by all immune individuals within the population) was not taken into account. However, herd immunity by vaccinating males would become important if vaccine coverage of women is likely to be less than 100% [56].

Fourth, regarding the assumption that the Markov model did not have the ability to remember the prior events, women with prior disease would have the same probability of redeveloping the disease as those without prior disease. On the contrary, from the previous clinical study [62], the probability of redeveloping the disease was higher in the women with prior disease. Therefore, this would make vaccine more favorable.

Lastly, our assumption was that a vaccination program would provide universal coverage to all 12-year-old girls rather than specific high-risk groups. Target-specific vaccination programs may be more cost-effective, but it is not straightforward and it might be untenable to reach all individuals at higher risk for HPV infection.

Conclusion

The model showed that the prophylactic quadrivalent vaccine was likely to be cost-effective in Thailand. These data are relevant for developing countries in deciding the best allocation of their limited health-care resources.

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